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GUEST EDITORIAL

The Significance of Clinical Trials and the Role of Meta-Analyses

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Much of the literature is turning attention to meta-analyses. This may be positive in light of the many underpowered studies that have been reported. However, one must step back and put this activity in perspective and not lose sight of the important role of the clinical trial in research.

Further elaboration on the meaning and role of meta-analysis will be forthcoming. First, it is appropriate to discuss or review the clinical trial. A clinical trial is a study designed to determine the safety and/or efficacy of a treatment or procedure. Safety is usually defined as toxicity or adverse event. Efficacy has many facets, such as response to therapy, response duration, survival, and quality of life. One may consider response as a change in a physical or clinical characteristic, such as reduction in blood pressure in hypertensive patients, disappearance or reduction of tumor growth or markers in cancer patients, improvement in physical functioning after a surgical procedure, and change in quality of life after an intervention. Change can be in terms of positive or negative (noneffi-cacy) outcomes.

A clinical study can be presented as a retrospective analysis—one in which past data or studies have been criticized as mostly inadequate due to selection bias of the data, being irrelevant to the current clinical setting or style of therapy delivery (e.g., more supportive care may be available today than in the past, thus influencing outcomes) and incomplete with respect to patient information that could bear on the overall outcome. There are many other reasons.

The choice is for the prospective clinical study, in which, if properly designed, both clinical and statistical considerations are well planned and controlled for. Prospective studies are longitudinal and require follow-up and well-planned evaluation. The phase I trial is a dose-seeking study in drug therapy so that one may obtain the maximum tolerable dose (MTD). The phase II trial attempts to determine some baseline response to a new therapy or intervention; if results are positive, one pursues a comparative efficacy trial of standard versus new therapy or procedure. The pilot study is often a small comparative trial in which one attempts to determine baseline efficacy of two procedures to determine if a larger comparative trial appropriately designed with adequate statistical power is feasible. Statistical power is discussed later.

Buyse et al. [1] edited a volume on all aspects of clinical studies in cancer research that applies to other areas of medicine as well. This is an excellent guide for the clinical researcher. The randomized phase III or prospective comparative trial is our focus.

The important considerations needed for the evaluation of the phase III trial are well-defined hypotheses, a detailed description of the study sample and the population from which it is drawn, the difference between the two treatments or interventions to be considered clinically meaningful, the type I error desired or the probability of falsely rejecting a null hypothesis of no treatment difference, and the power or probability of not rejecting a treatment effect when one truly exists. The type I error, difference to be desired, and power are the primary components of the statistical considerations of the phase III study. These three components contribute to determining the size of the sample or number of subjects needed on each treatment to adequately test the hypotheses. Thus, the size of the trial can be a critical issue, especially when an inadequate number of subjects have been put in a study—thus rendering the study inconclusive.

Herein lies the motivation for the meta-analysis. It is generally used when single trials yield inconclusive or conflicting results. It is also used when several trials (some may have inadequate sample size) asking a similar

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question have been performed and an overall conclusion is required. Colleagues and I [2] have defined meta-analysis as:

> " . . . the statistical analysis of a collection of analytic results for the purpose of integrating the findings. In medical terms the focus is on combining the results of several different studies that may not render in themselves a definitive conclusion concerning the superiority of one treatment over another. One may determine after combining these results if superiority in one direction does in fact exist."

This combination of results can include the combining of the actual data from the several studies or the summary data from the publications. Each has its advantages and disadvantages. The former, which is often called an "overview analysis" is generally preferred, as it omits some issues of bias such as publication bias in which not all studies dealing with the common issue may be published. Thus the results reported may include only results in favor of the alternative hypothesis (in many cases a positive trend), and the reader has no way of knowing what studies may have in fact been conducted showing an opposite trend. Assuming the most straightforward procedure of the overview analysis, there are still many problems to consider. Among them are that some studies may be better designed than others, and some may have been properly controlled and others not. Thus, in the attempt to summarize and recognize patterns of results there are inherent difficulties. Despite these concerns meta-analyses abound. For example, Mosteller and Chalmers [3], in their overview of meta-analyses, indicated that 16 meta-analyses per year were found in the scientific journals from 1983 to 1990. This figure has to be updated, but the trend is clear. This is a procedure that has reached a stage of general acceptance in the scientific literature. Dickersin and Berlin [4] have gone so far as to say that meta-analysis should be a standard tool; i.e., it should be performed when practical before new studies are undertaken or funded to ensure that investigators have a proper understanding of the gaps in the existing literature and of the relevant methodologic issues in the area. This is like having a quantitative literature and background review. Hogue [5] exercised a bit of caution and warned her readers of the inherent problems in database sharing. So it should be obvious to the reader that there are many considerations to be addressed prior to undertaking a meta-analysis. More detail on this subject is provided in the references cited as well as a more recent book by Hunt [6].

Not to be ignored are the types of statistical analyses used in a meta-analysis. There is nothing new here. Many of the standard statistical tests such as χ^2, z, and t-tests and analysis of variance are used. Several authors have discussed these procedures. Most notable is the work of Hedges and Olkin [7]. They have also outlined regression procedures to be used in a meta-analytic setting [8]. One of the major tasks of the meta-analytic user is to reconcile the problem of "heterogeneity." Heterogeneity occurs when the size or direction and the variance between the treatment and control group differ across the studies being considered. This makes it difficult statistically to combine a function of these differences, called the effect size, and to conclude that they share a common variance so that some traditional statistical tests may be performed. Chalmers [9] and Hedges and Olkin [7] address these issues. Thus, the statistical handling of these type of data have been and continue to be refined.

One of the more popular meta-analyses done in the clinical setting was that done by the Early Breast Cancer Trialists Collaborative Group [10], which was an overview of the randomized trials for tamoxifen for early breast cancer. The data were from 37,000 women in 55 such trials. This composed about 87% of the worldwide evidence. These results focused on 10-year recurrence and survival and presented evidence for various subgroups of prognoses, including estrogen receptor status, nodal status, time on tamoxifen (length of therapy), and age groupings. Other cancer type overview analyses can be found by referring to the Medical Research Council (MRC) [11] results. All these studies involve the cautions previously mentioned, and incorporate the statistical analyses outlined earlier as well. All are well done.

One has to keep in mind that many meta-analyses, simply due to the fact that they incorporate many studies and at times very large samples, will reach a statistically significant conclusion with very small differences. It is then up to the investigators reviewing the trials to determine if small differences that are statistically significant are in fact clinically significant. (This is where the cooperative effort of statistical and clinical investigators is very important, as it is in a randomized clinical trial.) A meta-analysis may best be viewed as scientific evidence in favor of or against a trend in treatment in the results being examined. For views on reader acceptance of a good meta-analysis and the things to look for when evaluating whether the meta-analysis has been done properly, see Bartolucci et al. [2] and Dickersin and Berlin [4].

The question naturally arises as to how meta-analyses compare to the prospectively randomized clinical trial. One must never abandon the clinical trial as the basis of good clinical research. In the past, authors such as Chalmers et al. [12] have attempted to compare the results of meta-analyses with single large cooperative trials. The results were mixed. Depending on the particular trial and the end point, meta-analysis agreed with the cooperative trial in some cases and disagreed on others. This is not surprising. First, the bias and heterogeneity

issues, as discussed earlier, are a challenge to the meta-analysis. Some trials favoring the control may not be included in the meta-analysis, resulting in some cases in which the meta-analysis favors the treatment and the cooperative study favors the control. It is difficult in some cases to have a meta-analysis that is all inclusive or includes a large majority of the studies, as is seen in the tamoxifen example. One also must keep in mind the purpose of the meta-analysis. Although we expect in many cases it will help to refine the precision of the treatment effect by integrating the results of many studies, we certainly hope that it will at least confirm the trend in the treatment performance.

In summary, the prospective randomized trial is the mainstay of clinical research. Meta-analysis has its role in helping to integrate these results. As has been the case in the past several years, we see that when one wishes to conduct a meta-analysis as in conducting a clinical trial, a team effort is required. This includes clinical, statistical, and other scientific experts in the field of interest so that all issues, their relevance, and interpretation can be evaluated appropriately.

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